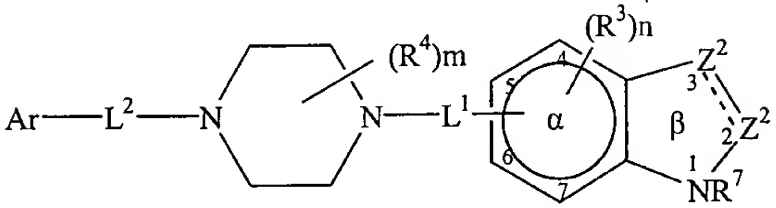
APPENDIX

1. A compound of the formula:



(1)

and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

 represents a single or double bond;

one Z^2 is CA or CR^8A and the other is CR^1, CR^1_2, NR^6 or N wherein each R^1, R^6 and R^8 is independently hydrogen or noninterfering substituent;

A is $-W_i-COX_jY$ wherein Y is COR^2 or an isostere thereof and R^2 is hydrogen or a noninterfering substituent, each of W and X is a spacer of 2-6Å which is substituted or unsubstituted alkylene, alkenylene or alkynylene, and each of i and j is independently 0 or 1;

R^7 is H or is optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, NR_2, OR, alkyl-SR, alkyl-SOR, alkyl-SO_2R, alkyl-OCOR, alkyl-COOR, alkyl-CN, alkyl-$CONR_2$, or R_3Si, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof;

each R^3 is independently a noninterfering substituent;

n is 0-3;

each of L^1 and L^2 is independently alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on L^1 or L^2 can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or

said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety;

each R^4 is independently a noninterfering substituent;

m is 0-4;

Ar is an aryl group substituted with 0-5 noninterfering substituents, wherein two noninterfering substituents can form a fused ring; and

the distance between the atom of Ar linked to L^2 and the center of the α ring is 4.5-24Å.

2. The compound of claim 1 wherein A is $COXjCOR^2$, and

wherein R^2 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^2 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is alkylene.

3. The compound of claim 1 wherein Y is an isostere of COR^2.

4. The compound of claim 3 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.

5. The compound of claim 1 wherein each of i and j is 0.

6. The compound of claim 2 wherein j is 0.

9. The compound of claim 1 wherein R^7 is H, or is optionally substituted alkyl, or acyl.

11. The compound of claim 1 wherein L^1 is CO, CHOH or CH_2.

12. The compound of claim 11 wherein L^1 is CO.

16. The compound of claim 1 wherein L^2 is unsubstituted alkylene and L^1 is CO.

17. The compound of claim 1 wherein L^2 is unsubstituted methylene, methylene substituted with alkyl, or -CH= and L^1 is alkylene or CO.

18. The compound of claim 1 wherein Ar is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

19. The compound of claim 18 wherein Ar is optionally substituted phenyl.

20. The compound of claim 19 wherein said optional substitution is by halo, OR, or alkyl.

21. The compound of claim 20 wherein said phenyl is unsubstituted or has a single substituent.

22. The compound of claim 1 wherein R^4 is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR,

$NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^4 on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or R^4 is =O or an oxime, oximeether, oximeester or ketal thereof.

23. The compound of claim 22 wherein each R^4 is halo, OR, or alkyl.

24. The compound of claim 23 wherein m is 0, 1, or 2.

25. The compound of claim 24 wherein m is 2 and both R^4 are alkyl.

26. The compound of claim 1 wherein each R^3 is halo, alkyl, heteroalkyl, OCOR, OR, NRCOR, SR, or NR_2, wherein R is H, alkyl, aryl, or heteroforms thereof.

27. The compound of claim 26 wherein R^3 is halo or alkoxy.

28. The compound of claim 27 wherein n is 0, 1 or 2.

29. The compound of claim 1 wherein L^1 is coupled to the α ring at the 4-, 5- or 6-position.

30. The compound of claim 1 wherein Z^2 at position 3 is CA or CHA.

31. The compound of claim 30 wherein the Z^2 at position 2 is CR^1 or CR^1_2.

32. The compound of claim 31 wherein R^1 is hydrogen, or is alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR, NR_2, SR, SOR, SO_2R, OCOR, NRCOR, $NRCONR_2$, NRCOOR, $OCONR_2$, RCO, COOR, alkyl-OOR, SO_3R, $CONR_2$, SO_2NR_2, $NRSO_2NR_2$, CN, CF_3, R_3Si, and NO_2, wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of R^1

can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

33. The compound of claim 32 wherein each R^1 is selected from the group consisting of H, alkyl, acyl, aryl, arylalkyl, heteroalkyl, heteroaryl, halo, OR, NR_2, SR, NRCOR, alkyl-OOR, RCO, COOR, and CN, wherein each R is independently H, alkyl, or aryl or heteroforms thereof.

34. The compound of claim 30 wherein Z^2 at position 2 is N or NR^6.

35. The compound of claim 34 wherein R^6 is H, or alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, or is SOR, SO_2R, RCO, COOR, alkyl-COR, SO_3R, $CONR_2$, SO_2NR_2, CN, CF_3, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof.

36. The compound of claim 1 wherein  represents a double bond.

37. The compound of claim 1 wherein the distance between the atom on Ar linked to L^2 and the center of the α ring is 7.5-11Å.

39. A pharmaceutical composition for treating conditions characterized by enhanced p38-α activity which composition comprises

a therapeutically effective amount of a compound claim 1 or the pharmaceutically acceptable salts thereof, along with a pharmaceutically acceptable excipient.

42. A method to treat rheumatoid arthritis comprising administering to a subject in need of such treatment a compound of claim 1 or the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof.

45. The compound of claim 36, wherein Z^2 at position 3 is CA.

46. The compound of claim 45, wherein Z^2 at position 2 is CR^1.

47. The compound of claim 46, wherein A is $COCOR^2$.

48. The compound of claim 47, wherein R^2 is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, CN, COOR, $CONR_2$, COR, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

wherein R^2 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$, or $NRSO_2NR_2$, wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR, NR_2, OCOR, NRCOR, $NRCONR_2$, $NRSO_2R$, $NRSO_2NR_2$, $OCONR_2$, or R_3Si wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined.

49. The compound of claim 48, wherein R^1 is H.

50. The compound of claim 49, wherein n is 0 or 1.

51. The compound of claim 50, wherein Ar is substituted phenyl.

52. The compound of claim 51, wherein L^2 is unsubstituted or substituted alkylene optionally including a heteroatom.

53. The compound of claim 52, wherein L^1 is alkylene or CO.

54. The compound of claim 53, wherein L^2 is methylene and L^1 is CO.

55. The compound of claim 54, wherein n is 1 and R^3 is halo or methoxy.

56. The compound of claim 55, wherein R^7 is H or alkyl.

57. The compound of claim 56, wherein R^7 is methyl.

58. The compound of claim 57, wherein Ar is para-fluorophenyl.

59. The compound of claim 58, wherein R^2 is OR, NR_2, SR, $NRCONR_2$, $OCONR_2$ or $NRSO_2NR_2$ wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom containing forms thereof and wherein two R attached to the same atom may form a 3-8 membered ring.

60. The compound of claim 59, wherein R^2 is NR_2 wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom containing forms thereof and wherein two R attached to the same atom may form a 3-8 membered ring.

61. The compound of claim 60, which is selected from the group consisting of compound Nos. 15, 33, 57, 59, 77, 89, 96, and 100 of Table 2, *i.e.*,

1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N-methyl-glyoxalicamide;

1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide;

1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide; and

1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide.

62. The compound of claim 60, wherein said compound is compound No. 15 of Table 2, *i.e.*, 1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

63. The compound of claim 60, wherein said compound is compound No. 33 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

64. The compound of claim 60, wherein said compound is compound No. 57 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

65. The compound of claim 60, wherein said compound is compound No. 59 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalicamide.

66. The compound of claim 60, wherein said compound is compound No. 77 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N-methyl-glyoxalicamide.

67. The compound of claim 60, wherein said compound is compound No. 89 of Table 2, *i.e.*, 1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

68. The compound of claim 60, wherein said compound is compound No. 96 of Table 2, *i.e.*, 1-methyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide.

69. The compound of claim 1, wherein said compound is compound No. 162 of Table 2, *i.e.*, 6-chloro-[4′-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

70. The compound of claim 60, wherein said compound is compound No. 100 of Table 2, *i.e.*, 1-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide.

71. The compound of claim 1, wherein said compound is compound No. 17 of Table 2, *i.e.*, 1-ethoxycarbonyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

72. The compound of claim 1, wherein said compound is compound No. 38 of Table 2, *i.e.*, 1-ethoxycarbonyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

73. The compound of claim 1, wherein said compound is compound No. 45 of Table 2, *i.e.*, 1-t-butoxycarbonyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

74. The compound of claim 1, wherein said compound is compound No. 56 of Table 2, *i.e.*, 1-acetyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

75. The compound of claim 1, wherein said compound is compound No. 60 of Table 2, *i.e.*, 1-acetyl-2-methyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

76. The compound of claim 1, wherein said compound is compound No. 63 of Table 2, *i.e.*, 1-methoxymethyl-6-chloro-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

77. The compound of claim 1, wherein said compound is compound No. 92 of Table 2, *i.e.*, 1-methoxymethyl-6-methoxy-[4′-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

78. The compound of claim 1, wherein said compound is compound No. 102 of Table 2, *i.e.*, 1-methyl-6-chloro-[4-(1-4'-fluorophenylethyl)piperazinyl]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

79. The compound of claim 1, wherein said compound is compound No. 137 of Table 3, *i.e.*, -methoxy-(4-benzyl piperazinyl)-indole-5-carboxamide-3-glyoxalic acid-methyl ester.

80. The compound of claim 1, wherein said compound is compound No. 138 of Table 3, *i.e.*, [4-(1-phenylethyl)piperazinyl]-indole-5-carboxamide-3-glyoxalic acid methyl ester.

81. The compound of claim 1, wherein said compound is compound No. 152 of Table 3, *i.e.*, (4-benzyl-2R,5S-piperazinyl)-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

82. The compound of claim 1, wherein said compound is compound No. 161 of Table 3, *i.e.*, 6-methoxy-[4'-fluoro-(4-benzyl-2,5-dimethyl piperazinyl)]-indole-5-carboxamide-3-glyoxalic acid-morpholinamide.

83. The compound of claim 1, wherein said compound is compound No. 177 of Table 3, *i.e.*, 6-methoxy-[4'-fluoro-(4-benzyl-2R,5S-dimethyl piperazinyl)]-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.

84. The compound of claim 1, wherein said compound is compound No. 180 of Table 3, *i.e.*, (6-methoxy[4-(1-4'-fluorophenylethyl)piperazinyl)-indole-5-carboxamide-3-N,N-dimethyl glyoxalicamide.